(11)

PATENT SPECIFICATION (21) 49,412 /72

Class (52) 09.15, 87.16

Int. Cl. (51) C07D 51/50

Application Number (21) 49412/72 Lodged (22) 29th November, 1972

Complete Specification entitled (54) A METHOD FOR PRODUCING 2-SUBSTITUTED ADENOSINE DERIVATIVES

Lodged (23) 29th November, 1972 ~~Accepted~~ (44) Lapsed Sec 47D (1)

Convention Priority (30) 1st December, 1971 Japan 97431/1971 24th January, 1972 Japan 8885/1972

Published (41) 30th May, 1974

Applicant (71) TAKEDA CHEMICAL INDUSTRIES, LTD.

Actual Inventor (72) YOSHIO YOSHIOKA, RUYJI MARUMOTO, MIKIO HONJO AND KATSUYOSHI KAWAZOE

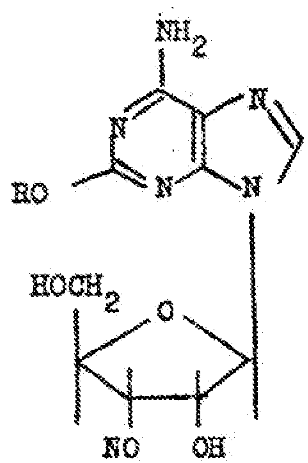
Related Art (56) Nil

The following statement is a full description of this invention, including the best method of performing it known to us :

The present invention relates to novel and useful adenosine derivatives, and to a method for producing these compounds.

It has been known that 2-methoxyadenosine has a hypotensive action as well as a coronary dilating action. However, this compound cannot be clinically used because of its low potency in said actions and of its rapid decomposition in blood.

The present inventors have succeeded in producing novel adenosine derivatives of the formula



(I)

wherein R is a lower alkyl group of not less than 2 carbon atoms; an ω-substituted polymethylene of the formula $R'O(CH_2)_{\underline{n}}-$ where R' is a hydrogen atom, a lower alkyl group or phenyl and n is an integer of from 2 to 6; or phenyl group which may be substituted with a lower alkyl group, a lower alkoxy group or a halogen atom, and further studies on these compounds (I) have unexpectedly revealed that they exhibit excellent pharmacological actions such as strong and prolonged coronary dilating and hypotensive actions.

Thus, the principal object of the present invention

is to provide the novel adenosine derivatives (I) as well as their pharmaceutically acceptable salts, which have the strong and long-lasting coronary dilating action as well as hypotensive action, and another object is to provide a pharmaceutical composition comprising one or more of these compounds. A further object is to provide a method for the production of the novel and useful adenosine derivatives (I) and their pharmaceutically acceptable salts.

Referring to the formula (I), the lower alkyl group of not less than 2 carbon atoms may be straight or branched chain and saturated or unsaturated, and may be advantageously those having up to 6 carbon atoms, which are exemplified by ethyl, n-propyl, isopropyl, allyl, n-butyl, isobutyl, crotyl, n-pentyl and n-hexyl.

The polymethylene moiety of the ω-substituted polymethylene represented by the formula $R'O(CH_2)_n$- includes ethylene, trimethylene, tetramethylene, pentamethylene and hexamethylene. R' in said formula is a hydrogen atom, a lower alkyl group or phenyl. The lower alkyl group for R' may be straight or branched chain and saturated or unsaturated, and may be advantageously those having up to 7 carbon atoms, which are exemplified by methyl, ethyl, propyl, isopropyl, allyl, n-pentyl and n-hexyl. As the typical examples of the ω-substituted polymethylene, there may be enumerated β-hydroxyethyl, β-methoxyethyl, β-ethoxyethyl, β-isopropoxyethyl, β-allyloxyethyl, β-n-butoxyethyl, β-n-heptyloxyethyl, β-phenoxyethyl, γ-hydroxypropyl, γ-ethoxy-n-propyl, γ-n-butoxy-n-propyl, γ-phenoxy-n-propyl, δ-hydroxy-n-

butyl, δ-methoxy-n-butyl, δ-n-butoxy-n-butyl, ε-hydroxy-n-pentyl, ε-methoxy-n-propyl, ε-n-propoxy-n-propyl, ζ-hydroxy-n-hexyl, ζ-methoxy-n-hexyl, ζ-ethoxy-n-hexyl and the like.

The phenyl group for R in the formula (I) may be substituted with a lower alkyl group, a lower alkoxy group or a halogen. The lower alkyl group as the substituent may be straight or branched chain and saturated or unsaturated, and may be advantageously that having up to 7 carbon atoms, which is exemplified by those mentioned above in connection with the lower alkyl group for R'. The lower alkoxy group may be advantageously that having up to 7 carbon atoms such as methoxy, ethoxy, n-propoxy, isopropoxy, allyloxy, n-butoxy and n-heptyloxy. The halogen atom may be any of chlorine, bromine, iodine and fluorine. The phenyl group may have one or more of these substituents at optional position or positions of the benzene ring. Representatives of the phenyl group having such a substituent or substituents are m-tolyl, p-ethylphenyl, p-n-butylphenyl, p-methoxyphenyl, p-n-propoxyphenyl, o-chlorophenyl, o-bromophenyl, o-fluorophenyl, m,m'-dichlorophenyl, p-ethyl-o-chlorophenyl and the like.

The adenosine derivatives of the formula (I) may be produced by, for example, reacting a 2-halogenoadenosine with a compound of the formula,

$$\mathrm{ROH} \qquad \text{(II)}$$

wherein R is as precedingly defined, in the presence of a base.

The 2-halogenoadenosine is a <u>per se</u> known compound

and may be easily prepared by, for example, the method described in "Journal of Heterocyclic Chemistry", 1, pp.213-214. 2-chloroadenosine or 2-bromoadenosine may be most conveniently employed as the 2-halogenoadenosine.

As the base, there may be advantageously employed an inorganic base such as hydroxides of alkali metals or of alkali earth metals (e.g., sodium hydroxide, potassium hydroxide, lithium hydroxide, calcium hydroxide and barium hydroxide) or alkali metals *per se* (e.g. sodium metal and potassium metal). Thus, throughout the present specification as well as appended claims the term "inorganic base" includes alkali metals.

When an alkali metal is employed, it is preferable to dissolve the alkali metal in the compound of the formula (II), which is an alcohol or a phenol, and to allow the resulting alkoxide or phenoxide to act upon the 2-halogenoadenosine. In this instance, it is advantageous to dissolve, relative to one mol of 2-halogenoadenosine, about 1 to 10 mols, most advantageously about 5 to 7 mols, of an alkali metal in a large excess (e.g. about 10 to 300 mols) of the compound (II) and permit the resulting solution to act upon the 2-halogenoadenosine. The excess of the compound (II) plays also the role of a solvent, but, if desired, there may be employed an organic solvent such as dioxane, dimethylsulfoxide and a mixture thereof.

When a hydroxide of an alkali metal or of an alkali earth metal is employed, it is preferable to similarly dissolve the hydroxide of solid state in the compound (II) and to allow the resulting solution to act upon the halogenoadenosine. In this case, too, it is

advantageous to dissolve, relative to one mol of the 2-halogenoadenosine, about 1 to 10 mols, most advantageously about 5 to 7 mols, of the hydroxide in a large excess (e.g. about 10 to 300 mols) of the compound (II).

The above-mentioned reaction proceeds smoothly at a temperature of from about 50° to about 200°C, especially, from about 100° to about 130°C. For this reaction, anhydrous conditions are not necessarily required, and the reaction proceeds even in the presence of a small amount, e.g. up to an equimolar amount relative to the 2-halogenoadenosine, of water in the reaction system.

By the said reaction, the halogen atom of the 2-halogenoadenosine is replaced with RO- group derived from the compound (II) to form the adenosine derivative of the formula (I). Thus-produced adenosine derivatives (I) can be easily recovered from the reaction mixture and purified by a *per se* known means such as extraction, recrystallization, chromatography and the like. The adenosine derivatives (I) can be converted into their pharmaceutically acceptable salts by a *per se* conventional means. The typical examples of the pharmaceutically acceptable salts are mineral acid salts such as hydrochloride, sulfate and the like.

When a compound of the formula (II) in which R is the lower alkyl group of not less than 2 carbon atoms is employed, there is observed a tendency that a 2-alkoxy-adenosine oligomer is produced as a secondary product. In this instance, the object compound (I) can be easily separated from the 2-alkoxy-adenosine oligomer by a

conventional separation means such as precipitation from an aqueous solution or chromatography (e.g. silica gel column chromatography).

The novel adenosine derivatives (I) and the pharmaceutically acceptable salts thereof are characterized by their strong and long-lasting coronary dilating action as well as hypotensive action, and may be used as coronary dilating and/or hypotensive agents for mammals.

The following is an example of the test in which the coronary dilating action of illustrative compounds of the present invention is demonstrated.

Test for coronary dilating action

Mongrel dogs of either sex, weighing from 7 to 10 kg., were anesthetized with sodium pentobarbital (intravenous administration of 30 mg./kg.). Under artificial respiration with room air the chest was opened through the fifth left intercostal space. After heparinization (1,000 units/kg., intravenously), the circumflex branch of the left coronary artery was proximally ligated, and the distal segment was immediately cannulated with a polyethylene cannula and perfused with the blood flowing from the left carotid artery through an electric flowmeter. Each test compound was injected into the coronary artery or the femoral vein of the animals in the form of a 0.1 mg/ml. solution in water or in a mixture of water and polyethylene glycol at the dose of 10 µg. per animal for the intracoronary injection or of 10 µg./kg. for the intravenous injection. The increase in coronary flow after the injection was measured with regard to the respective test compounds and percent

coronary flow increase in each period of time set forth in Tables 1 and 2 below was calculated according to the following equation :

$$\left(\frac{\text{Maximum coronary flow in the period} - \text{coronary flow before the injection}}{\text{Coronary flow before the injection}} \right) \times 100 = \text{percent coronary flow increase}$$

The results are summarized in Tables 1 and 2 below.

TABLE 1 (Intracoronary injection)

Test Compound	Percent coronary flow increase		
	0-05 minute after injection	0.5-1 minute after injection	1 - 2 minutes after injection
2-methoxyadenosine	137.4	35.7	12.8
2-n-propoxyadenosine	227.8	175.3	143.1
2-n-butoxyadenosine	260.0	133.9	107.8
2-n-pentyloxyadenosine	192.5	90.0	60.0
2-allyloxyadenosine	175.8	89.2	59.4
2-crotyloxyadenosine	138.5	69.2	46.2
2-(β-hydroxyethoxy)-adenosine	261.3	141.1	83.7
2-(β-methoxyethoxy)-adenosine	237.4	62.8	32.6
2-(β-ethoxyethoxy)-adenosine	245.3	105.7	72.4
2-phenoxyadenosine	186.0	60.3	39.4

TABLE 2 (Intravenous injection)

Test Compound	Percent coronary increase		
	0 – 1 minute after injection	1 – 2 minutes after injection	2 – 3 minutes after injection
2-methoxyadenosine	0	0	0
2-ethoxyadenosine	81.7	63.3	37.5
2-n-propoxyadenosine	133.2	156.7	95.9
2-n-butoxyadenosine	102.8	49.6	49.8
2-n-pentyloxyadenosine	100.0	64.7	23.5
2-(β-hydroxyethoxy)-adenosine	143.6	66.2	35.4
2-(β-ethoxyethoxy)-adenosine	105.8	81.4	50.9
2-(β-n-butoxyethoxy)-adenosine	60.0	20.0	20.0
2-phenoxyadenosine	51.4	17.4	7.2
2-(m-methylphenoxy)-adenosine	61.4	18.5	7.7

The adenosine derivatives (I) and their pharmaceutically acceptable salts may be administered alone or in combination with a pharmaceutically acceptable carrier or carriers. They are administrable in the forms of powders, tablets, solutions or emulsions for oral administration, or in the form of injectable liquid.

Pharmaceutical compositions containing one or more

of the present compounds can be prepared by per se conventional methods for the preparation of powder, capsules, tablets, pills, injections and the like. The choice of carriers may be determined depending upon the route of administration, the solubility of the adenosine derivatives (I) and so on.

The dose of the compounds of the present invention may be chosen depending upon the route of administration, the species of mammals and purpose of administration. For instance, when the present compounds are orally administered to a human adult for the purpose of treating coronary insufficiency or essential hypertension, advantageous doses are in a range from 0.1 mg. to 20 mg. per day.

The following Examples are intended merely to illustrate presently preferred embodiments of the present invention and not to restrict the scope of this invention.

Throughout the foregoing description as well as in the following Examples and Claims, "μg.", "mg.", "kg.", "ml." and "°C" respectively refer to "microgram(s)", "milligram(s)", "kilogram(s)", "milliliter(s)" and "degrees centigrade". In Examples, the relationship between parts by weight and parts by volume corresponds to that between grams and milliliters.

EXAMPLE 1

In 50 parts by volume of 2-methoxyethanol is dissolved 1.0 part by weight of sodium metal, followed by the addition of 4.53 parts by weight of 2-chloroadenosine. The mixture is heated at 130°C for 4 hours, after which time the reaction mixture is concentrated to

dryness. The residue is dissolved in 20 parts by volume of water and the solution is adjusted to pH 7.0 with acetic acid to give precipitates. The precipitates recovered by filtration are dissolved in 100 parts by volume of a mixture of methanol and chloroform (3:17 by volume) and the solution is allowed to pass through a column packed with 80 parts by weight of silica gel. The effluent is concentrated under reduced pressure to obtain 3.30 parts by weight of 2-(β-methoxyethoxy)adenosine as white plates melting at 179°C.

Ultraviolet absorption spectrum

$\lambda_{max}^{0.1N\text{-}HCl}$ mμ(ε): 273(11.6x10^3), 248(8.1x10^3);

$\lambda_{max}^{H_2O}$ mμ(ε): 266(12x10^3); $\lambda_{max}^{0.1\text{-}NaOH}$ mμ(ε): 266(11.9x10^3)

Elementary analysis

Calculated for $C_{13}H_{19}N_5O_6$	
	C, 45.74%; H, 5.61%; N, 20.52%
Found	C, 45.53%; H, 5.72%; N, 20.41%

EXAMPLE 2

The procedure of Example 1 is duplicated except that 5.21 parts by weight of 2-bromoadenosine is used in place of 2-chloroadenosine and the reaction time is 2 hours. The procedure yields 3.52 parts by weight of 2-(β-methoxyethoxy)adenosine as plates melting at 179°C.

EXAMPLE 3

The procedure of Example 1 is duplicated except that 1.0 part by weight of potassium metal is used in place of sodium metal. This procedure yields 3.5 parts by weight of 2-(β-methoxyethoxy)adenosine as plates

melting at 179°C.

EXAMPLE 4

In 200 parts by volume of 2-methoxyethanol are dissolved 2.00 parts by weight of 2-chloroadenosine and 2.00 parts by weight of solid sodium hydroxide, and the solution is heated at 120°C for 2 hours. The reaction mixture is subjected to the same isolation treatment as described in Example 1, whereupon 1.1 part by weight of 2-(β-methoxyethoxy)adenosine is obtained as plates melting at 179°C.

EXAMPLE 5

4.5 parts by weight of 2-chloroadenosine, 40 parts by volume of ethylene glycol monobutyl ether and 1.0 part by weight of sodium metal are reacted under the same conditions as described in Example 1.

After cooling to 20°C, to the reaction mixture is added 200 parts by volume of diethyl ether to give precipitates. The precipitates recovered by filtration are dissolved in 1,000 parts by volume of 20% methanol. After being adjusted to pH 7.0 with 1N-hydrochloric acid, the solution is treated with a column of activated carbon (45 parts by weight). The column is washed with 2,000 parts by volume of water and eluted with a mixture of pyridine, ethanol, concentrated aqueous ammonia and water (50:50:1:49 by volume). The eluate is concentrated to dryness and the residue is dissolved in 20 parts by volume of methanol, followed by the addition of 200 parts by volume of diethyl ether. The resulting precipitates are recovered by filtration to obtain 3.5 parts by weight of 2-(β-n-butoxyethoxy)adenosine as white powder.

Ultraviolet absorption spectrum

$\lambda_{max}^{0.1N-HCl}$ mu(ε): 273(11.9×10^3), 248(8.2×10^3);

$\lambda_{max}^{H_2O}$ mu(ε): 266(12.2×10^3); $\lambda_{max}^{0.1N-NaOH}$ mu(ε): 267(12.2×10^3)

Elementary analysis

Calculated for $C_{16}H_{25}N_5O_6$

C, 50.12%; H, 6.57%; N, 18.27%

Found C, 49.80%; H, 6.56%; N, 18.05%

EXAMPLE 6

In a mixture of 30 parts by volume of phenol and 30 parts by volume of dioxane, there is dissolved 1.0 part by weight of sodium metal, followed by the addition of 4.53 parts by weight of 2-chloroadenosine. The mixture is stirred at 120°C for 8 hours. After the reaction mixture is cooled to 20°C, it is poured in 600 parts by volume of diethyl ether. The resulting precipitates are recovered by filtration and purified by the column chromatography employing silica gel under similar conditions to those set forth in Example 1. The procedure yields 2.95 parts by weight of 2-phenoxyadenosine as white powder.

Ultraviolet absorption spectrum

λ_{max}^{MeOH} mu(ε): 266(14.3×10^3)

Elementary analysis

Calculated for $C_{16}H_{17}N_5O_5\cdot\frac{1}{2}CH_3OH\cdot\frac{1}{2}H_2O$

C, 51.56%; H, 5.24%; N, 18.22%

Found C, 51.94%; H, 4.99%; N, 17.90%

EXAMPLE 7

3.0 parts by weight of solid sodium hydroxide is dissolved in 300 parts by weight of ethanol on heating,

followed by the addition of 4.5 parts by weight of 2-chloroadenosine. The mixture is boiled for 3 hours, and then concentrated under reduced pressure to dryness. The residue is dissolved in 20 parts by volume of water and the solution is adjusted to pH 7.0 with acetic acid. The resulting precipitates are removed away by filtration and the filtrate is concentrated under reduced pressure to dryness. The solution of the residue in 100 parts by volume of methanol is subjected to filtration and the resulting filtrate is allowed to pass through a column packed with 30 parts by weight of silica gel. The column is eluted with 2,000 parts by volume of a mixture of methanol and chloroform (1:9 by volume). The first 500 parts by volume fractions are discarded and all the subsequent fractions are pooled and concentrated to dryness. The residue is dissolved in 20 parts by volume of methanol followed by the addition of 100 parts by volume of diethyl ether. The procedure yields 3.0 parts by weight of 2-ethoxy-adenosine as white powder.

Ultraviolet absorption spectrum

$\lambda_{max}^{0.01N-HCl}$: 275, 249mμ; $\lambda_{max}^{H_2O}$: 268,253(shoulder)mμ

Elementary analysis

Calculated for $C_{12}H_{17}N_5O_5 \cdot \frac{1}{2}H_2O$

	C, 45.00%;	H, 5.66%;	N, 21.87%
Found	C, 45.07%;	H, 5.26%;	N, 21.84%

EXAMPLE 8

A mixture of 4.5 parts by weight of 2-chloroadenosine, 100 parts by volume of n-propanol and 4.0 parts by weight of solid sodium hydroxide is stirred at 120°C for

10 hours. The reaction mixture is subjected to the same isolation procedure as described in Example 7 to obtain 2-n-propoxy-adenosine as white powder.

Ultraviolet absorption spectrum

$$\lambda_{max}^{0.01N\text{-}HCl}: 275, 249 m\mu; \lambda_{max}^{H_2O}: 268, 253 (shoulder)\ m\mu$$

Elementary analysis

Calculated for $C_{13}H_{19}N_5O_5 \cdot \frac{1}{2}H_2O$

	C, 46.69%;	H, 6.03%;	N, 20.95%
Found	C, 46.80%;	H, 5.53%;	N, 20.85%

EXAMPLE 9

A mixture of 1 part by weight of 2-chloroadenosine, 100 parts by volume of n-butanol, 5.0 parts by weight of sodium hydroxide and 0.5 parts by volume of water is heated at 100°C for 2 hours. The reaction mixture is concentrated under reduced pressure to dryness and the resulting residue is dissolved in 10 parts by volume of water. The solution is adjusted to pH 7.0 with 1N-hydrochloric acid and concentrated under reduced pressure to dryness. The residue is extracted with 150 parts by volume of 2-methoxymethanol on heating and the extract is subjected to column-chromatography on silica gel as in Example 7 to obtain 0.4 part by weight of 2-n-butoxy-adenosine as white powder. This product is recrystallized from water to obtain 0.3 part by weight of colorless needles melting at 155°C.

Elementary analysis

Calculated for $C_{14}H_{21}N_5O_5$

	C, 49.55%;	H, 6.24%;	N, 20.64%
Found	C, 49.36%;	H, 6.06%;	N, 20.84%

A solution of 1 part by weight of thus obtained 2-n-butoxyadenosine in 20 parts by volume of methanol is added to 3.5 parts by volume of 1N-hydrochloric acid to give 0.9 part by weight of 2-n-butoxyadenosine hydrochloride as white powder.

EXAMPLE 10

A mixture of 1.0 part by weight of 2-chloro-adenosine, 100 parts by volume of n-butanol and 4.5 parts by weight of potassium hydroxide is heated at 90°C for 1 hour. The reaction mixture is subjected to the same isolation procedure as described in Example 9 to obtain 0.3 part by weight of 2-n-butoxyadenosine as colorless needles melting at 155°C.

EXAMPLE 11

A mixture of 1.0 part by weight of 2-bromoadenosine, 100 parts by volume of amyl alcohol, 4 parts by weight of calcium hydroxide and 0.5 part by volume of water is heated at 100°C for 2 hours. The reaction mixture is subjected to the same isolation procedure as described in Example 9 to obtain 0.15 part by weight of 2-n-pentyloxy-adenosine as white powder.

Ultraviolet absorption spectrum

$$\lambda_{max}^{0.01N\text{-}HCl} : 275, 249\ m\mu; \lambda_{max}^{H_2O} : 268, 253 (\text{shoulder})\ m\mu$$

Elementary analysis

Calculated for $C_{15}H_{23}N_5O_5$

	C, 50.98%;	H, 6.56%;	N, 19.82%
Found	C, 50.69%;	H, 6.66%;	N, 19.91%

EXAMPLE 12

1.0 part by weight of sodium metal is dissolved in a mixture of 30 parts by volume of allyl alcohol and

50 parts by volume of dioxane, followed by the addition of 5.0 parts by weight of 2-chloroadenosine. The resulting solution is boiled for 4 hours. The reaction mixture is subjected to the same isolation procedure as described in Example 7 to obtain 0.8 part by weight of 2-allyloxyadenosine as colorless needles melting at 193°C.

Elementary analysis

Calculated for $C_{13}H_{17}N_5O_5$

	C, 48.29%;	H, 5.30%;	N, 21.66%
Found	C, 48.41%;	H, 5.48%;	N, 21.73%

EXAMPLE 13

The same procedures as in the preceding Examples are repeated to obtain the compounds listed in Table 3, which are novel and useful and fall within the scope of the formula (I).

TABLE 3

Compound	Elementary analysis			Melting point, Ultraviolet absorption spectrum
	Molecular Formula	Calculated (%)	Found (%)	
2-(β-ethoxyethoxy)-adenosine	$C_{14}H_{21}N_5O_6 \cdot \frac{1}{2}H_2O$	C 46.15 H 6.09 N 19.23	C 46.02 H 6.07 N 19.05	$\lambda^{0.1N-HCl}_{max}$: 273,248mμ $\lambda^{H_2O}_{max}$: 266,250(shoulder)mμ $\lambda^{0.1N-NaOH}_{max}$:266,250(shoulder)mμ
2-(β-phenoxyethoxy)-adenosine	$C_{18}H_{21}N_5O_6 \cdot 1/4H_2O$	C 53.00 H 5.31 N 17.17	C 53.17 H 5.18 N 16.97	$\lambda^{C_2H_5OH}_{max}$; 269 mμ (ε = 13.8×10^3) $\lambda^{C_2H_5OH}_{min}$: 234 mμ
2-(β-hydroxyethoxy)-adenosine	$C_{12}H_{17}N_5O_6 \cdot \frac{1}{2}H_2O$	C 38.71 H 5.94 N 18.81	C 38.86 H 5.64 N 19.15	$\lambda^{0.1N-HCl}_{max}$: mμ (ε); 274(12.0×10^3), 248(8.4×10^3) $\lambda^{H_2O}_{max}$ mμ(ε); 266(12.2×10^3) $\lambda^{0.1N-NaOh}_{max}$:mμ (ε); 267(12.4×10^3)

TABLE 3 (cont'd)

2-(m-methylphenoxy)-adenosine	$C_{17}H_{19}N_5O_5 \cdot H_2O$	C 52.17 H 5.41 N 17.90	C 52.34 H 5.05 N 17.97	Melting point: 131° - 132°C
2-(p-methoxyphenoxy)-adenosine	$C_{17}H_{19}N_5O_6 \cdot \frac{1}{2}H_2O$	C 51.25 H 5.05 N 17.58	C 51.58 H 4.84 N 17.26	Melting point: 155° - 157°C λ_{max}^{MeOH} mμ(ε); 252 (shoulder), 267(15.3x10^3), 277(shoulder)
2-(o-chlorophenoxy)-adenosine	$C_{16}H_{16}N_5O_5Cl \cdot H_2O$	C 46.66 H 4.40 N 17.00	C 46.53 H 4.42 N 16.61	Melting point; 148° - 150°C
2-(β-n-heptyloxy-ethoxy)adenosine	$C_{19}H_{32}N_5O_6$	C 53.51 H 7.56 N 16.42	C 53.90 H 7.28 N 16.71	$\lambda_{max}^{0.1N-HCl}$; 273,247 mμ $\lambda_{max}^{H_2O}$; 266 mμ $\lambda_{Max}^{0.1N-NaOH}$;266 mμ

TABLE 3 (cont'd)

2-(ζ-hydroxy-n-hexyloxy)adenosine	$C_{16}H_{25}N_5O_6$	C 50.12 H 6.57 N 18.27	C 49.77 H 6.50 N 18.58	$\lambda_{max}^{0.1N-HCl}$; 247,274 mμ $\lambda_{max}^{H_2O}$; 267 mμ $\lambda_{max}^{0.1N-NaCh}$;266mμ
2-(δ-hydroxy-n-butoxy)adenosine	$C_{14}H_{21}N_5O_6$	C 47.32 H 5.96 N 19.71	C 47.65 H 6.03 N 19.45	$\lambda_{max}^{0.1N-HCl}$; 273,246mμ $\lambda_{max}^{H_2O}$;266mμ $\lambda_{max}^{0.1N-NaOH}$; 267mμ
2-ethoxyadenosine	$C_{12}H_{17}N_5O_5 \cdot \frac{1}{2}H_2O$	C 45.00 H 5.66 N 21.87	C 45.07 H 5.26 N 21.84	$\lambda_{max}^{0.1N-HCl}$; 275,249 mμ $\lambda_{max}^{H_2O}$; 268,253 (shoulder)mμ

TABLE 3 (cont'd)

2-isopropoxy-adenosine	$C_{13}H_{19}N_5O_5 \cdot \frac{1}{2}H_2O$	C 46.69 H 6.03 N 20.95	C 46.92 H 5.67 N 20.73	$\lambda_{max}^{0.1N-HCl}$; 273,248mμ $\lambda_{max}^{0.1N-NaOH}$; 267mμ
2-n-hexyloxy-adenosine	$C_{16}H_{25}N_5O_5$	C 52.30 H 6.86 N 19.06	C 52.71 H 6.54 N 18.83	$\lambda_{max}^{0.1N-HCl}$; 273,248mμ $\lambda_{max}^{0.1N-NaOH}$; 266mμ
2-crotyloxy-adenosine	$C_{14}H_{19}N_5O_5$	C 49.84 H 5.68 N 20.76	C 50.34 H 5.79 N 20.16	NMR spectrum (d_6-DMSO) δ; 1.7(3H,singlet,methyl), 4.7(3H,m,$H_{2'}$, $-CH_2O-H$, 5.8(3H,m,$H_{1'}$, $-CH=CH-$)

EXAMPLE 14

Some examples of practical recipes in which the compounds of this invention are utilized as coronary dilating and/or hypotensive agents are as follows:

A. (Tablet)

(1)	2-n-butoxyadenosine	20 mg.
(2)	lactose	35 mg.
(3)	corn starch	150 mg.
(4)	microcrystalline cellulose	30 mg.
(5)	magnesium stearate	5 mg.
		240 mg. per tablet

(1), (2), (3), 2/3 quantity of (4) and half quantity of (5) are thoroughly mixed, and then the mixture is granulated. Remaining 1/3 quantity of (4) and half of (5) are added to the granules and compressed into tablets. Thus prepared tablets can further be coated with a suitable coating agent, e.g. sugar.

B. (Capsule)

(1)	2-phenoxyadenosine	20 mg.
(2)	lactose	102 mg.
(3)	microcrystalline cellulose	70 mg.
(4)	magnesium stearate	8 mg.
		200 mg. per capsule

(1), (2), (3) and half quantity of (4) are thoroughly mixed, and then the mixture is granulated. Remaining half of (4) is added to the granules and the whole is filled into a gelatin capsule.

C. (Injection)

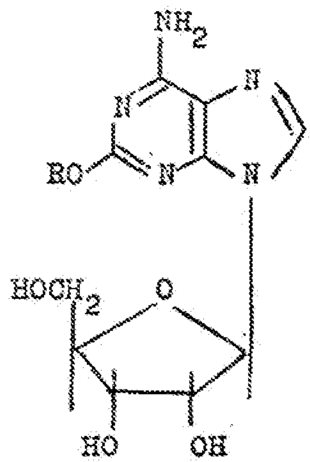
(1)	2-(β-methoxyethoxy)adenosine	10 mg.
(2)	inositol	100 mg.
(3)	benzyl alcohol	20 mg.

All ingredients are dissolved in water to make 2.0 ml. of the solution (pH 7.5) serving as injection.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

Having thus disclosed the invention, what is claimed is:

1. An adenosine derivative of the formula



wherein R is a lower alkyl group of not less than 2 carbon atoms; an ω-substituted polymethylene of the formula $R'O(CH_2)_n$- where R' is a hydrogen atom, a lower alkyl group or phenyl and n is an integer of from 2 to 6; or phenyl group which may be substituted with a lower alkyl group, a lower alkoxy group or a halogen atom, and pharmaceutically acceptable salts thereof.

2. An adenosine derivative as claimed in claim 1, wherein the pharmaceutically acceptable salt is a mineral acid salt.

3. An adenosine derivative as claimed in claim 2, wherein the mineral acid salt is a hydrochloride.

4. An adenosine derivative as claimed in claim 1, wherein R is a lower alkyl group of not less than 2 carbon atoms.

5. An adenosine derivative as claimed in claim 4, wherein the lower alkyl group has from 2 to 6 carbon atoms.

6. An adenosine derivative as claimed in claim 1,

wherein R is an ω-substituted polymethylene of the formula $R'O(CH_2)_n$- where R' is a hydrogen atom, a lower alkyl group or phenyl and n is an integer of from 2 to 6.

7. An adenosine derivative as claimed in claim 6, wherein R' is a lower alkyl group having up to 7 carbon atoms.

8. An adenosine derivative as claimed in claim 6, wherein n is 2.

9. An adenosine derivative as claimed in claim 1, wherein R is phenyl group which may be substituted with a lower alkyl group, a lower alkoxy group or a halogen atom.

10. An adenosine derivative as claimed in claim 9, wherein the phenyl group is substituted with a lower alkyl group having up to 7 carbon atoms.

11. An adenosine derivative as claimed in claim 9, wherein the phenyl group is substituted with a lower alkoxy group having up to 7 carbon atoms.

12. An adenosine derivative as claimed in claim 1, which is 2-n-propoxyadenosine.

13. An adenosine derivative as claimed in claim 1, which is 2-n-butoxyadenosine.

14. An adenosine derivative as claimed in claim 1, which is 2-n-pentyloxyadenosine.

15. An adenosine derivative as claimed in claim 1, which is 2-(β-hydroxyethoxy)adenosine.

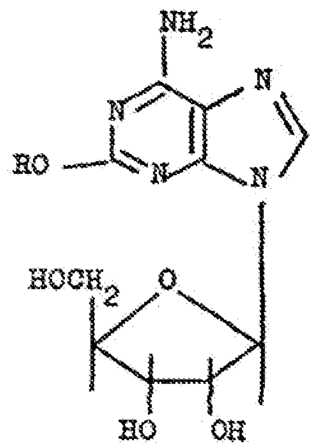
16. An adenosine derivative as claimed in claim 1, which is 2-(β-methoxyethoxy)adenosine.

17. An adenosine derivative as claimed in claim 1, which is 2-(β-ethoxyethoxy)adenosine.

18. An adenosine derivative as claimed in claim 1,

which is 2-(m-methylphenoxy)adenosine.

19. A method for producing an adenosine derivative of the formula



(I)

wherein R is a lower alkyl group of not less than 2 carbon atoms; an ω-substituted polymethylene of the formula $R'O(CH_2)_{\underline{n}}$- where R' is a hydrogen atom, a lower alkyl group or phenyl and n is an integer of from 2 to 6; or phenyl group which may be substituted with a lower alkyl group, a lower alkoxy group or a halogen atom, or its pharmaceutically acceptable salts, which comprises reacting a 2-halogenoadenosine with a compound of the formula

ROH (II)

wherein R is as precedingly defined in the presence of a base.

20. A method as claimed in claim 19, wherein the pharmaceutically acceptable salt is a mineral acid salt.

21. A method as claimed in claim 20, wherein the mineral acid salt is a hydrochloride.

22. A method as claimed in claim 19, wherein the base is an inorganic base.

23. A method as claimed in claim 22, wherein the inorganic base is a hydroxide of an alkali metal or of an

alkali earth metal.

24. A method as claimed in claim 22, wherein the inorganic base is an alkali metal.

25. A method as claimed in claim 19, wherein the 2-halogenoadenosine is reacted with an alkoxide or phenoxide produced from the compound of the formula (II) and an alkali metal.

26. A method as claimed in claim 19, wherein the 2-halogenoadenosine is 2-chloroadenosine or 2-bromoadenosine.

27. A method as claimed in claim 19, wherein R is a lower alkyl group of not less than 2 carbon atoms.

28. A method as claimed in claim 27, wherein the lower alkyl group has from 2 to 6 carbon atoms.

29. A method as claimed in claim 19, wherein R is an ω-substituted polymethylene of the formula $R'O(CH_2)_n$- where R' is a hydrogen atom, a lower alkyl group or phenyl and n is an integer of from 2 to 6.

30. A method as claimed in claim 29, wherein R' is a lower alkyl group having up to 7 carbon atoms.

31. A method as claimed in claim 29, wherein n is 2.

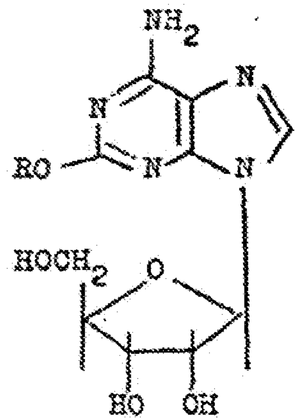
32. A method as claimed in claim 19, wherein R is phenyl group which may be substituted with a lower alkyl group, a lower alkoxy group or a halogen atom.

33. A method as claimed in claim 32, wherein the phenyl group is substituted with a lower alkyl group having up to 7 carbon atoms.

34. A method as claimed in claim 32, wherein the phenyl group is substituted with a lower alkoxy group having up to 7 carbon atoms.

35. A pharmaceutical composition which comprises, as the

active ingredient, at least one adenosine derivative of the formula



wherein R is a lower alkyl group of not less than 2 carbon atoms; an ω-substituted polymethylene of the formula $R'O(CH_2)_{\underline{n}}$- where R' is a hydrogen atom, a lower alkyl group or phenyl and $\underline{n}$ is an integer of from 2 to 6; or phenyl group which may be substituted with a lower alkyl group, a lower alkoxy group or a halogen atom, or its pharmaceutically acceptable salts together with a pharmaceutically acceptable carrier therefor.

36. A pharmaceutical composition as claimed in claim 35, wherein the pharmaceutically acceptable salt is a mineral acid salt.

37. An adenosine derivative as claimed in claim 36, wherein the mineral acid salt is a hydrochloride.

DATED this 28th day of November, 1972.

TAKEDA CHEMICAL INDUSTRIES, LTD.
By their Patent Attorney:

54.

of GRIFFITH, HASSEL & FRAZER.